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| 10/757,827 | 01/15/2004 | Michael R. Rosen | 13533/48003 | 5518 |

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| EXAMINER | |
|---|---|
| SINGH, ANOOP KUMAR | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/757,827 | ROSEN ET AL. | |
| | Examiner | Art Unit | |
| | ANOOP SINGH | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *20,49,51,57,59 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,49,51,57,59 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' amendment to the claims filed January 26, 2009 has been received and entered. Applicants have amended claims 49, 51, 57, 59, 65-67, while claims 1-19, 21-48, 50, 52-56, 58 and 60-64 have been canceled. Applicants have also added claim 68 that is generally directed to elected invention. Claims 20, 49, 51, 57, 59, 65-68 are pending in this application.

This action is non-Final.

### *Election/Restrictions*

Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group was found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

Claims 20, 49, 51, 57, 59, 65-68 are under consideration in the instant application.

### *Claim Rejections- 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 57, 59, 66-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a method of expressing a functional HCN2 ion channel in the mammalian heart, said method comprising, site specifically introducing the composition comprising an autologous or allogeneic mesenchymal stem cell comprising a nucleic acid encoding HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is directly introduced by injection into the heart, microinjection or cardiac catheterization; such that said composition forms gap junction with the cells of the heart; thereby expressing the functional ion channel in the mammalian heart,

(ii) a method of inducing a pacemaker current in a mammal's heart, said method comprising, site specifically introducing a composition comprising an autologous or allogeneic mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is directly introduced by injection into the heart, microinjection or cardiac catheterization; such that said composition forms a gap junction with the cells of the heart; thereby inducing a pacemaker current in the cells of the heart,

(iii) a method of inducing pacemaker current in a cardiomyocyte, said method comprising, contacting a cardiomyocyte with a composition comprising an autologous or allogeneic mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is contacted by injection into the heart, microinjection or cardiac catheterization; wherein said composition forms gap junction with the MSC; thereby inducing a pacemaker current in the cardiomyocyte,

does not reasonably provide enablement for a method for expressing ion channel or inducing current in the mammal's heart using xenogeneic MSC transplantation. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's amendments and previously submitted declaration by Dr. Rosen on May 3, 2008 have been fully considered and are persuasive. In view of Applicants' amendments of the base claims limiting to "introducing the composition by injection, microinjection or catheterization", the previous rejections of claims over these issues are hereby withdrawn. Further, applicants' argument that instant claims are enabled for treating a cardiac rhythm disorder in a mammal is also persuasive. Therefore, rejection pertaining to this issue is withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot. However, upon further consideration a new rejection is applied to claims 49, 57, 59, 66-67 that is presented below.

It is noted that claims 49, 57, 59, 66-67 embrace injecting genetically modified xenogenic MSC derived from any source intended to induce pacemaker current in a mammal. The claimed invention as recited will encompass autologous, allogeneic as well as xenogeneic transplantation, however, these transplantation methods are not routine. The art summarized by the references of Samstein et al (Journal of American Society of Nephrology 12: 182-193, 2001) and Sprangers et al (Kidney Int. 2008; 74(1):14-21) noted that for non-autologous cells, the most serious challenge is the destruction of cell implant by the host's immune system and that in xenografts; complement mediation is the major problem whereas the hyper acute rejection is the rapid and dramatic immunological response. The specification does not teach how to address the issues of hyperacute and complement mediation associated with the xenotransplantation of cells. In fact post filing art also discloses that xenogeneic transplantation of cells was not routine and had multiple problem including the immune response of the recipient to the transplant, the physiologic limitations of the transplant and infection. It is relevant to point out that prior to instant invention, Grinnemo et al indicated the potential of graft rejection in a xenogenic

model when adult hMSC is transplanted (see Grinnemo et al J Thorac Cardiovasc Surg. 2004 May; 127(5):1293-300, page 1298, col. 2, last para, art of record). It is noted that although Plotnikov (Circulation 116:706713, 2007,art of record) in post filing art provided survival of graft up to 42 days, however, instant specification does not provide any guidance with respect to binding of canine IgG to the surface of hMSCs ( as shown in Plotnikov Figure 6D) or contemplated measuring infiltration by $CD3^+$ T lymphocytes (Figure 6E) to establish whether or not method of claims 57, 59, 66 and 67 that read on xenogenic transplant would survive in the mammal. It is noted that several years after filing of this application, Plotnikov emphasizes that MSC have the potential to differentiate into more mature cell types. Plotnikov states "If this occurs, it is reasonable to question whether the cells will maintain their immunoprivileged status. Given this possibility, it is important to ensure that hMSCs remain in an undifferentiated state for use as biological pacemakers and/or that evidence be obtained to determine whether maturation and differentiation cause immunoprotection to be lost and rejection to occur". Thus, it is apparent that the disclosure in the specification at best is limited to a method of expressing a functional HCN2 and a method of inducing pacemaker current in heart using autologous or allogeneic MSC. The specification fails to extrapolate these finding to a method of using xenogeneic MSC in inducing pacemaker current or formation of gap junctions as several issues including graft survival were not resolved at the time of filing of this application. Furthermore, art of record teaches use of autologous cells to prevent an immune response, which otherwise with xenogeneic cells may exacerbate the already ischemic heart tissue. Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation.

***Withdrawn-Claim Rejections - 35 USC § 103***

Claims 20 and 65 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pittenger et al (US 6,387,369, dated 2002, ref of record), Jansen et al (US 6,979,532, dated 12/27/2005, effective filing date 2/12/2000, art of record) and Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005, art of record). Applicant's arguments have been fully considered and are persuasive. Therefore, the rejection is hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot. However, upon further consideration a new rejection is made that is set forth below.

***New-Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 49, 51, 57, 59, 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (USP 7,494,644, dated 2/24/2009, effective filing date 11/7/2002), and Qu et al (Circulation res. 2001, 89:e9, IDS).

Claims are directed to a composition comprising a mesenchymal stem cell that is genetically modified with a nucleic acid encoding HCN2. Subsequent claim limit the MSC to include human MSC. Claims are also directed to a method of preparing the composition comprising MSC that is genetically modified to express HCN2 and introducing directly into the heart by injection, wherein MSC form gap junction, thereby treating cardiac rhythm disorder or induce pacemaker current.

With respect to claims 20, 65 and 68, Lee et al teach a composition comprising a recombinant mammalian cell that is genetically engineered to express connexin 43(Cx43) protein intended for establishing electrical coupling between

cardiomyocytes and recombinant mammalian cells, wherein the mammalian cells are mesenchymal stem cells. It is reported that the cell may be autologous or allogeneic to the host including human that requires transplantation of genetically modified cell (see col. 14, lines 47-55). Lee et al also teach that Cells may be autologous, allogeneic, or xenogeneic with respect to the host. Thus, teaching of Lee embraces using human mesenchymal stem cell to treat a host that is human (see col. 14, lines 56-60, col. 5, line 21, col. 10, line 8).

Regarding claims 49, 57, 59, 66 and 67, Lee et a teach a method of establishing electrical coupling between cardiomyocytes and recombinant mammalian cells which have been genetically engineered to express a connexin 43 (Cx43) protein, wherein the mammalian cells are mesenchymal stem cells (e.g. claims 1 and 2). It is noted that Lee et al teach that "electrical coupling" means the interaction between cells which allows for intracellular communication between cells so as to provide for electrical conduction between the cells in which electrical excitation of cells through gap junction in the muscle leads to muscle contraction (see col. 10, 20-25). Thus, method of stabling electrical coupling for inducing current is accomplished by injecting MSC to cardiomyocyte in the heart to express the transgene so as to provide for electrical conduction through formation of gap junction meeting the limitation of claims.

Regarding claim 51, Lee et al teach a method for treating a cardiac conduction disturbance in a host, the method comprising: introducing into cardiac tissue of said host a therapeutically effective amount of a recombinant mammalian cell genetically modified to express a connexin 43 proteins; wherein the recombinant mammalian cell is a mesenchymal stem cell, and wherein the cell is autologous or allogeneic to the host, wherein said introducing is performed by injection into cardiac tissue of the host, or is performed by cardiovascular infusion into the host, and wherein said introducing is effective to establish an electrical connection between the recombinant cell and a myocardial cell of the host cardiac tissue; and

wherein the cardiac conduction disturbance in the host is treated (see claim 8). It is noted that in a preferred embodiment Lee et al report that the host is a human. Further, Lee teaches the methods may also be utilized in combination with other cardiac therapies when appropriate.

While Lee et al teach all the limitation of the pending claims, but differed from claimed invention by not disclosing MSC comprising nucleic acid encoding HCN2.

The deficiency of Lee is cured by Qu who reported an adenoviral construct comprising nucleic acid encoding HCN2. Qu et al teach treatment of both adult and neonatal cells in culture with the AdHCN2 construct resulted in expression of high current levels, with faster activation in neonate (Figures 1B and 1C) (see page 2, col. 2, para. 3).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the composition disclosed by Lee by substituting the gene of interest to HCN2 as disclosed by Qu. One of ordinary skill in the art would be motivated to do use HCN2 as Qu had already shown that HCN2 could be expressed in mammalian cells to induce pacemaker current. One of ordinary skill in the art would reasonably conclude that the composition would implicitly form gap junction when directly administered to the heart of a subject particularly since Lee taught hMSCs engrafts in the myocardium and forms gap junction with recipient MCS (supra). Therefore, given that MSC including human MSC were available for use to express gene of interest as per the teachings of Lee, it would have obvious for one of ordinary skill in the art to substitute Cx43 with another gene such as HCN2 to produce transformed MSC cells in the method of disclosed by Lee. One who would practice the invention would have reasonable expectation of successfully practicing the composition comprising mesenchymal stem cell incorporated with HCN2 in a method of inducing pacemaker current, forming gap junction or treating rhythm disorder because the art had already shown that hMSC forms electrical coupling

with cardiomyocytes and gene or small molecule could be delivered to the heart cells or cardiomyocyte. One of skill in the art would have had a reasonable expectation of success in combining the teachings because Lee et al had already disclosed establishing electrical coupling between cardiomyocytes and genetically modified mesenchymal stem cells, while Qu provided relevant information about a construct comprising HCN2 for inducing pacemaker current in the heart cells. Further more, it was routine in the art at the time of filing to genetically modify mesenchymal stem cells by substituting the coding sequence of one transgenes with another gene of interest.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

***Maintained- Double Patenting***

Claims 20, 49, 51, 57, 59, 65-66 and 67 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 39, 65, 67-68, 73-76, of copending Application no 10/342506 (US Patent Publication no 20040137621) in view of Jansen et al (US 6,979,532). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass similar composition and method steps of inducing current and /or treating a cardiac condition by introducing a composition of mesenchymal stem cell comprising a nucleic acid encoding HCN2 into a subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. As indicated by applicants a Terminal disclaimer later would obviate this rejection.

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-

type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

## *Conclusion*

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Pittenger et al (US 6,387,369, dated 2002, ref of record).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632